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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/220,142	12/23/1998	STEPHEN H. FRIEND	9301-035-999	3869

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EXAMINER	
MARSCHEL, ARDIN H	

ART UNIT	PAPER NUMBER
1631	31

DATE MAILED: 06/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No. 09/220,142	Applicant(s) FRIEND ET AL.	
	Examiner Ardin Marschel	Art Unit 1631	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 27 December 2002 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *27 December 2002*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *of reasons as attached*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ ~~For purposes of Appeal~~, the proposed amendment(s) a)☐ will not be entered or b)☒ ~~will be~~ has been entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *None*.

   Claim(s) objected to: *14,18,22,26,47,50,61,64,92,96,106,119 and 123*.

   Claim(s) rejected: *1,3-13,15-17,19-21,23-25,27-46,48,49,58-60,62,63,72-78,89-91,93-95,97-100,105,107-118,120-122 and 124*.

   Claim(s) withdrawn from consideration: *None*.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☒ Other: *Attachment: Exr. Int. Sum. (Paper No. 30)*

6.6.03

Continuation of 3. Applicant's reply has overcome the following rejection(s): All rejection based on 35 U.S.C. 112 in the action, mailed 6/27/02.

Further Explanation of Item 5 on the attached Advisory Action:

The rejection of claims 1, 3-8, 10-13, 15-17, 19-21, 23-25, 27-46, 48, 49, 58-60, 62, 63, 72-78, 89-91, 93-95, 97-100, 105, 107-113, 115-118, 120-122, and 124 under 35 U.S.C. § 103(a) based on Eisen et al.[PNAS 95:14863(1998)] is maintained from the final office action, mailed 6/27/02. Applicants firstly argue that each of a collection of different drug perturbations, as resulting in up-regulation or down-regulation of gene sets, are not taught or suggested in Eisen et al. This argument was responded to previously in that different serum additions are reasonably different drug perturbations. It is also noted that nothing in the instant claims requires different drug(s) per se for each perturbation, thus deemed inclusive of different drug additions as performed in Eisen et al. Applicants then argue that the perturbations of Eisen et al. are not drug perturbations. In response there is no instant definition of what a drug is that distinguishes the drug(s) as instantly claimed from the biological material, such as serum, in Eisen et al. It is recognized that the serum of Eisen et al. clearly perturbs the yeast cells in the reference and thus is reasonably a drug, which is generally a material which exhibits perturbational effects on cells. It is additionally pointed out that the suggestion and motivation to study what are specifically

referred to as drug targets by the Eisen et al. method was pointed out in the previous office action, mailed 10/9/01, as being set forth in the introductory paragraphs on page 14863 and not responded to in applicants' recent arguments. It is well known in the art that drug targets are targets which respond to drug administration or perturbation. Applicants then argue that merely displaying and analyzing data under different perturbations does not make the claimed invention obvious. Firstly , this seems to be an admission by applicants that different perturbations are, in fact, set forth in Eisen et al. Secondly, and in response, it is unclear what argument is meant thereby as no specific argument is noted in such a statement other than a broad allegation which is therefore non-persuasive. Applicants then state that genes are clustered in different sets in the reference and not in general co-varying under different perturbations. In response this argument is contrary to the clear showing of co-variance of genes in the reference over different serum perturbations and thus a non-persuasive argument. Applicants then argue that Eisen et al. does not teach or suggest the up- or down-regulation of genes by each perturbation. In response this argument is also contrary to the display of data in Figures 1-3 of the reference where intensity of colored boxes in the reference are clearly correspondent to up- or down-regulation

of genes in genesets, analyzed via expression, as clustered as previous pointed to in the reference. Applicants then argues at length regarding this same up- or down-regulation aspect of co-varying genes. This has been responded to and no further distinct argument is seen as having been set forth by applicants. Applicants then argue regarding projected vs. supervised response profiles but does not point to a distinguishing definition as filed and thus this argument is also non-persuasive. Applicants then argue that the determination of correlation coefficients is different from a determination of statistical significance and point to the instant specification at pages 25, lines 10-21, as defining a similarity metric, and page 28, line 27, through page 33, line 16. Consideration of page 25, lines 10-21, firstly reveals that there is no discussion that this is a similarity metric, nor that the therein defined correlation coefficient is distinct from what is meant by "statistical significance". Additionally, a correlation coefficient is clearly described in said page 25 citation as an embodiment of the instant invention. The citation on page 28, line 27, through page 33, line 16, starts with the header "Statistical Significance" but nowhere in this citation is there any distinction defined that limits such significance to be distinct from a correlation coefficient calculation practice. Also, on page 28, lines 28-29, the

practice of an objection testing of statistical significance is described as a "Preferably" type of practice which thus is not limiting but only preferred out of a broader set of testing for clustering practice, therefore deemed to include correlation coefficient determinations. Additionally, the statistical significance argument is moot as this does not occur as a limitation in any of the above rejected claims. It is, however, noted that a "similarity metric" is a limitation of instant claim 39 which has been admitted by applicants as being a correlation coefficient practice in their arguments. Thus, clearly supporting this rejection on this issue. Applicants then again argue that Eisen et al. does not teach of grouping of expression effects into response profiles. In response the Figures 1-3 and related discussion that has been pointed to above and in previous office actions already have thoroughly responded regarding this allegation as not been persuasive and therefore no further response is deemed needed to this reiterated argument. Applicants then argue that the reference lacks a determination of therapeutic efficacy of a drug. In response the effect of drug perturbation(s) has been responded to above as well as in previous office actions as being described for serum as a broadly defined type of drug as well as for drugs per se regarding their

effects on drug targets. Thus, this argument has already been responded to.

Welsh is then argued as not filling in what is lacking in Eisen et al. In response, as discussed above, Eisen et al. suggests and motivates the basics of the instant invention and thus Welsh is not needed to fill in any lacking description, suggestion, or motivation, for the basics of the instant invention, contrary to the allegation of applicants. This argument also reiterates the arguments regarding co-varying cellular constituent in response to different drug perturbations, response profiling, statistical significance determination, therapeutic efficacy determination, and grouping or clustering of gene responses; which are not further commented here due to being fully responded to above, as well as in previous office actions. It is noted that the added argument regarding the profiling of at least 5 profiles is set forth in this section of arguments. In response, Figure 1 of Eisen et al. depicts 12 different profiles corresponding to 12 perturbations which clearly describes the "at least 5" argument and is therefore also non-persuasive. To reiterate and summarize the rejection based on the combination of Eisen et al. in view of Welsh, Welsh was set forth in combination with Eisen et al. to add only the suggestion

and motivation to study drug toxicity along with dosing or treatment in drug targeting practice.

Claims 1, 3-13, 15-17, 19-21, 23-25, 27-46, 48, 49, 58-60, 62, 63, 72-78, 89-91, 93-95, 97-100, 105, 107-118, 120-122, and 124 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Eisen et al.[PNAS 95:14863(1998), taken in view of Welsh (P/N 5,686,114). This rejection is maintained as being argued and responded to above in connection with the rejection based on Eisen et al.

Due to the withdrawl of the rejections based on 35 U.S.C. § 112; claims 14, 18, 22, 26, 47, 50, 61, 64, 92, 96, 106, 119, and 123 are now objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No claim is allowed.

INFORMALITY

Applicants have set forth a clean version of the pending claims in Exhibit B, filed 12/27/02. Consideration of this Exhibit B has revealed that it has omitted pending claim 30. A review of the prosecution history of the instant application has failed to reveal any previous cancellation of claim 30.

Applicants are requested to include claim 30 in any future such listings, unless claim 30 is canceled.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703)308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., whose telephone number is (703)308-3894. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703)308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (703)305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

June 6, 2003

Ardin J Marschel